Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy


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Background: This multicenter randomized trial compared oral capecitabine with bolus i.v. 5-fluorouracil (5-FU)/folinic acid (FA) as adjuvant therapy for stage III colon cancer.

Patients and methods: Patients were assigned to 24 weeks of capecitabine 1250 mg/m² twice daily on days 1–14 every 3 weeks or 5-FU/FA (Mayo Clinic regimen). The primary end point was disease-free survival (DFS).

Results: The intent-to-treat population received capecitabine (𝑛 = 1004) or 5-FU/FA (𝑛 = 983). With a median follow-up of 6.9 years, capecitabine was at least equivalent to 5-FU/FA in terms of DFS [hazard ratio (HR) = 0.88; 95% confidence interval (CI) 0.77–1.01] and overall survival (OS) [HR = 0.86; 95% CI 0.74–1.01]; the 95% CI upper limits were significantly less than the predefined noninferiority margins of 1.20 (𝑃 < 0.0001) and 1.14 (𝑃 < 0.001), respectively. This pattern was maintained in all subgroups, including patients aged ≥70 years. Preplanned multivariate analyses showed that capecitabine had statistically significant beneficial effects on DFS (𝑃 = 0.021) and OS (𝑃 = 0.020) versus 5-FU/FA. A post hoc analysis suggested that the occurrence of hand–foot syndrome may be associated with better outcomes in capecitabine recipients.

Conclusion: Oral capecitabine is an effective alternative to bolus 5-FU/FA as adjuvant treatment of patients with stage III colon cancer with efficacy benefits maintained at 5 years and in older patients.

Key words: 5-fluorouracil/folinic acid, adjuvant therapy, capecitabine, colon cancer, elderly, pharmacodynamic markers

Introduction

The benefits of adjuvant chemotherapy on overall survival (OS) in patients with resected node-positive (stage III) colon cancer are well established [1–4]. By the late 1990s, a 6-month regimen of bolus 5-fluorouracil (5-FU)/folinic acid (FA; i.e. Mayo Clinic or Roswell Park) had emerged as the standard adjuvant treatment of patients with stage III colon cancer [5–9].

The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT; M66001) trial was initiated in November 1998 to compare the efficacy of the oral fluoropyrimidine capecitabine (Xeloda®, F. Hoffmann-La Roche Inc., Basel, Switzerland) and bolus 5-FU/FA (Mayo Clinic regimen) as adjuvant therapy in patients with curatively resected stage III colon cancer. The primary efficacy analysis, which demonstrated that capecitabine was at least equivalent to 5-FU/FA in terms of 3-year disease-free survival [DFS; hazard ratio (HR) 0.87; 95% confidence interval (CI) 0.75–1.00], has been reported previously [10], as have the safety data [10, 11].

Here, we report definitive efficacy data from the X-ACT trial with median follow-up of 6.9 years, including the first analysis of treatment at relapse. In addition, following preliminary data indicating that the benefits of adjuvant therapy with the newer chemotherapy agents might be limited to those aged <70 years [12], we report outcomes in the X-ACT trial by age.

The importance of dose modifications in ‘tailoring’ capecitabine treatment of the individual patient has been demonstrated [13]. An earlier report suggested that patients with metastatic breast cancer treated with capecitabine who develop hand–foot syndrome (HFS) may have better outcomes [14]; we undertook, therefore, a post hoc analysis exploring the relationship between HFS and updated efficacy outcomes in the X-ACT trial.
patients and methods

The X-ACT trial, which has been described previously [10], was conducted in accordance with the Declaration of Helsinki and its amendments. Approval of the protocol was obtained at each participating site from an Ethics Review Committee or Institutional Review Board. All patients provided written informed consent before study participation.

patient eligibility

Patients aged 18–75 years with histologically confirmed stage III colon carcinoma, an Eastern Cooperative Oncology Group performance status of zero or one, and life expectancy of ≥5 years were eligible. Surgery with curative intent was carried out within 8 weeks before study randomization, by which time patients were required to be fully recovered from surgery.

study design and treatment plan

X-ACT was a multicenter, randomized, open-label, parallel-group phase III study designed with a primary end point of showing at least equivalence in terms of DFS between capecitabine and bolus 5-FU/FA. Secondary efficacy end points were OS and relapse-free survival (RFS).

Patients received 24 weeks’ treatment with either oral capecitabine 1250 mg/m² twice daily on days 1–14 of a 21-day cycle (i.e. eight cycles) or a rapid i.v. infusion of FA 20 mg/m² followed immediately by i.v. bolus 5-FU 425 mg/m² on days 1–5 of a 28-day cycle (i.e. six cycles).

Randomization was stratified by center.

efficacy evaluation

Abdominal and pelvic computed tomography or magnetic resonance imaging and thoracic radiography were carried out every 6 months for 2 years and annually thereafter. DFS, the primary study end point, was defined as the time between randomization and first relapse, the occurrence of a second primary colon cancer, death from any cause, or the last date at which the patient was known to be disease free. RFS was defined as the time between randomization and the first relapse, occurrence of a second primary colon cancer, death due to treatment-related adverse events or colon cancer if relapse had not been reported. OS was defined as the time from randomization to death or the date at which the patient was last confirmed to be alive.

statistical analysis

The intention-to-treat population included all patients who underwent randomization; only data for this population are presented in this report.

The primary efficacy analysis was planned when 632 events (relapse, new occurrence of colon cancer or death) had occurred [10]. The secondary 5-year efficacy analysis, which was prospectively planned, was carried out in August 2007 and is reported herein.

For this analysis, a noninferiority margin of 1.20 was predefined for DFS; noninferiority was concluded if the upper limit of the 95% CI of the HR was ≤1.20. For OS, a noninferiority margin of 1.14 was predefined. For both end points, tests for superiority using the Wald chi-squared test were planned if the initial noninferiority analyses were positive.

DFS, RFS and OS were presented as Kaplan–Meier estimates and HRs with 95% CIs. Planned multivariate analyses to evaluate the robustness of the data with respect to DFS and OS were based on proportional hazards regression. Potentially clinically relevant factors were identified from previous trials [3, 4, 8]. Subgroup analyses were also prospectively planned. In addition, the effect of dose modifications on DFS was investigated.

HFS: post hoc analysis, grading and management

A post hoc analysis of the potential relationship between the occurrence of HFS and DFS or OS was carried out using Cox regression.

HFS was graded as follows: grade 1—numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema not disrupting normal activities; grade 2—painful erythema with swelling that affects daily activities; and grade 3—moist desquamation, ulceration, blistering or severe pain leading to an inability to work or perform daily activities.

In the event of grade 2 or 3 HFS, treatment was to be interrupted promptly until symptoms resolved or decreased in intensity to grade 1. Following grade 3, or the second appearance of grade 2, HFS, capecitabine was continued at 75% of the original dose. Following the second appearance of grade 3, or the third appearance of grade 2, HFS, capecitabine was continued at 50% of the original dose. Treatment was discontinued after any further occurrence of HFS. These dose modifications are in keeping with the Capecitabine Summary of Product Characteristics.

results

patient population and follow-up

A total of 1987 patients were randomized to capecitabine (n = 1004) or 5-FU/FA (n = 983) between November 1998 and November 2001; they constituted the intent-to-treat population (Figure 1). The baseline characteristics of patients were very similar in the two treatment groups. Slightly more patients in the capecitabine arm had carcinoembryonic antigen (CEA) levels above the upper limit of normal (9% versus 7% in the 5-FU/FA arm) and stage N2 disease (i.e. involvement of ≥4 regional lymph nodes) (31% versus 29%), but these differences were not statistically significant. There were 396 patients aged ≥70 years.

Overall, 90% (n = 343) and 87% (n = 350) of patients randomized to capecitabine and 5-FU/FA, respectively, received ≥1 therapeutic intervention at relapse. A similar proportion of patients received systemic treatments at relapse in the two randomization arms (capecitabine versus 5-FU/FA); these included 5-FU (57% versus 49%), oxaliplatin (41% versus 35%), irinotecan (36% versus 41%), raltitrexed (6% versus 6%) and cetuximab (4% versus 5%). Capecitabine, however, was later given to more patients in the 5-FU/FA versus capecitabine arm (24% versus 14%). Locoregional procedures were carried out at relapse in a similar proportion of patients in the capecitabine versus 5-FU/FA arms, including radiotherapy (18% versus 19%), partial hepatectomy (9% versus 9%) and laparotomy (9% versus 5%).

Median follow-up, calculated as the time from randomization to clinical cut-off (4 June 2007), was 6.9 years in both treatment groups. At this time, 319 patients (32%) in the capecitabine arm and 351 patients (36%) in the 5-FU/FA arm had died.

disease-free survival

The efficacy results in the intent-to-treat population are summarized in Table 1. After a median follow-up of 6.9 years, capecitabine was at least equivalent to bolus 5-FU/FA in terms of DFS (the primary end point; Figure 2A). The HR for DFS for capecitabine versus 5-FU/FA was 0.88 (95% CI 0.77–1.01), the upper limit of the 95% CI being significantly below the predefined noninferiority margin of 1.20 (P < 0.0001). A subsequent predetermined test for superiority showed a clear trend (P = 0.07) towards superior DFS in patients randomized to capecitabine versus 5-FU/FA. The 5-year DFS rates for capecitabine and 5-FU/FA were 60.8% and 56.7%, respectively.
Similarly, RFS was at least equivalent for patients in the capecitabine arm compared with those in the 5-FU/FA arm. There was a trend towards superior RFS in patients receiving capecitabine, although this did not reach statistical significance (HR 0.89, 95% CI 0.78–1.02; P = 0.104; Figure 2B). The 5-year RFS rates for patients receiving capecitabine and 5-FU/FA were 63.2% and 59.8%, respectively.

Overall survival
In this updated analysis, capecitabine was also at least equivalent to 5-FU/FA in terms of OS. The HR for OS for capecitabine versus 5-FU/FA was 0.86 (95% CI 0.74–1.01; Figure 2C); the upper limit of the 95% CI was significantly less than the predefined noninferiority margin of 1.14 (P < 0.001). The test for superiority showed a trend (P = 0.06) towards superior OS in patients receiving capecitabine versus 5-FU/FA. The 5-year OS rates for capecitabine and 5-FU/FA were 71.4% and 68.4%, respectively.

Multivariate analysis
The unadjusted analysis was confirmed in a multivariate analysis by adjusting for important predefined factors significantly associated with improved outcomes (i.e. female sex, stage N1 disease and normal baseline CEA levels for both DFS and OS and younger age for OS). After adjustment, capecitabine had a statistically significant beneficial effect on both DFS and OS compared with 5-FU/FA (Table 2).

Subgroup analyses
Subgroup analyses of OS showed a consistent trend towards benefit for patients randomized to receive capecitabine versus 5-FU/FA for all prognostic factor subgroups (Figure 3). There was no significant interaction for treatment by age with respect to either DFS (P = 0.50) or OS (P = 0.78). This included patients aged ≥70 years in whom the 5-year OS rate was 68.8% and 65.0% (HR 0.91, 95% CI 0.65–1.26) for those treated with capecitabine and 5-FU/FA.

Table 1. Efficacy after a median follow-up of 6.9 years (intent-to-treat population)

<table>
<thead>
<tr>
<th>End point</th>
<th>Number of patients</th>
<th>Number of patients with event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value for equivalence</th>
<th>P value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>Capecitabine</td>
<td>1004</td>
<td>421</td>
<td>0.88 (0.77–1.01)(^a)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>5-FU/FA</td>
<td>983</td>
<td>452</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse-free survival</td>
<td>Capecitabine</td>
<td>1004</td>
<td>389</td>
<td>0.89 (0.78–1.02)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>5-FU/FA</td>
<td>983</td>
<td>413</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>Capecitabine</td>
<td>1004</td>
<td>319</td>
<td>0.86 (0.74–1.01)(^b)</td>
<td>0.000116</td>
</tr>
<tr>
<td></td>
<td>5-FU/FA</td>
<td>983</td>
<td>351</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Noninferiority was concluded if the upper limit of the 95% CI was <1.20. 
\(^b\)Noninferiority was concluded if the upper limit of the 95% CI was <1.14. 
CI, confidence interval; 5-FU, 5-fluorouracil; FA, folinic acid.
respectively; the corresponding DFS rates were 58.1% and 55.8% (HR 0.97, 95% CI 0.72–1.31), respectively (Table 3).

treatment and dose modifications
The planned course of treatment was completed by 83% of patients in the capecitabine arm (85% aged <70 years; 74% aged ≥70 years) and 87% of patients in the 5-FU/FA arm (89% aged <70 years; 83% aged ≥70 years). Dose modification (i.e. dose reduction or delay/interruption of treatment) was required by 57% (55% aged <70 years; 65% aged ≥70 years) and 52% (50% aged <70 years; 61% aged ≥70 years) of patients randomized to capecitabine and 5-FU/FA, respectively. Dose reduction was required by 42% (39% aged <70 years; 51% aged ≥70 years) and 44% (42% aged <70 years; 54% aged ≥70 years) of patients randomized to capecitabine and 5-FU/FA, respectively. The efficacy of neither capecitabine nor 5-FU/FA appeared to be compromised in patients who required dose modifications (Figure 4).

relationship between efficacy and HFS
All-grade treatment-related HFS occurred in 62% of patients in the capecitabine arm and 10% of patients in the 5-FU/FA arm (P < 0.001); grade 1/2 HFS was observed in 44% and 9% (P < 0.001) and grade 3 HFS in 17% and 0.6% (P < 0.001) of patients receiving capecitabine and 5-FU/FA, respectively.

Figure 2. Disease-free survival (A), relapse-free survival (B) and overall survival (C) in patients receiving capecitabine or 5-fluorouracil/folinic acid (intent-to-treat population).

Table 2. Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.002 (0.995–1.009)</td>
<td>0.6043</td>
</tr>
<tr>
<td>Gender (female versus male)</td>
<td>0.775 (0.672–0.894)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Regional lymph nodes (PN1 versus PN0, PN2, PNx)</td>
<td>0.621 (0.536–0.718)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline CEA (below versus above ULN)</td>
<td>0.426 (0.345–0.525)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time from surgery to randomization (days)</td>
<td>1.003 (0.996–1.009)</td>
<td>0.4166</td>
</tr>
<tr>
<td>Treatment effect (capecitabine versus 5-fluorouracil/folinic acid)</td>
<td>0.849 (0.739–0.976)</td>
<td>0.0212</td>
</tr>
</tbody>
</table>

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; ULN, upper limit of normal.
5-FU/FA in terms of 5-year OS. The results of the unadjusted (main) analysis, which showed a trend towards better OS with capecitabine versus 5-FU/FA, were further supported by the predefined multivariate analysis that demonstrated a statistically significant improvement in outcome for patients randomized to receive capecitabine. The trend towards improved OS with capecitabine can be attributed to the greater efficacy of capecitabine with confidence as there were no apparent differences in either locoregional or systemic treatments given at relapse to patients in the two arms of the X-ACT trial.

When evaluating the results of a randomized trial, it is important to look at outcomes in the control arm compared with other studies using the same regimen. It is recognized that intertrial comparisons have clear limitations but do provide some historical information regarding the efficacy of therapeutic interventions. Nevertheless, in this regard, the results with the Mayo Clinic regimen in X-ACT are consistent with those of the large Intergroup 0089 trial [5]. That trial included a mixed patient population with stage II (19% of patients) or stage III (81%) disease, whereas the X-ACT trial was limited to those with stage III disease. The Intergroup trial reported a 5-year DFS rate of 60% and an OS rate of 66% [5] compared with rates of 57% and 68%, respectively, in the present study for those randomized to 5-FU/FA. We can, therefore, be confident that outcomes in patients receiving 5-FU/FA in the X-ACT trial were as expected and the benefits of capecitabine robust.

In routine clinical practice, a significant proportion of patients are ≥70 years old and the recent preliminary ACCENT analysis [12] suggested that ‘newer’ adjuvant regimens (combinations with irinotecan/oxaliplatin or oral fluoropyrimidines) are not associated with significant efficacy benefits versus 5-FU/FA in older patients; indeed, it was suggested that these patients may have worse outcomes with the newer adjuvant regimens. These conclusions should not, however, be applied to capecitabine. The prospective subanalysis by age in the X-ACT study showed a trend towards improved efficacy with capecitabine compared with 5-FU/FA in all age groups, including patients ≥70 years. This is relevant as the addition of oxaliplatin may be less attractive in older patients because of concerns about toxicity and lack of evidence that efficacy is maintained [12]. It has been shown previously that the pattern of toxicity is similar for capecitabine and 5-FU/FA in patients aged ≥70 years in the X-ACT trial [16]. We therefore suggest that capecitabine is an appropriate choice for those aged >70 years as well as younger patients.

While bolus 5-FU/FA was recognized as the optimal adjuvant regimen for patients with colon cancer when the protocol for the X-ACT trial was devised, the toxicity of these regimens, and particularly that of the Mayo Clinic regimen, has been well documented. Infusional 5-FU regimens are now often favored because they offer similar or slightly improved efficacy than bolus 5-FU/FA regimens and are generally better tolerated.
However, the plasma concentration profile of capecitabine, which is given twice daily for 14 days, more closely resembles that of a continuous infusion of 5-FU than daily or weekly bolus 5-FU injections. A cross-trial comparison of the X-ACT and MOSAIC trials [19], which used LV5FU2 (de Gramont regimen) as the control group, suggests that capecitabine has similar efficacy to infusional 5-FU/FA. After a median follow-up of 6 years, the rate of OS for patients with stage III disease reported with LV5FU2 (68.7%) [19] was almost identical to that observed with capecitabine (68.4%) in the X-ACT trial.

Safety data from the X-ACT trial, which have been reported previously [10, 11], show that capecitabine has an improved safety profile compared with bolus 5-FU/FA in terms of significantly lower rates of diarrhea, stomatitis, nausea, alopecia, neutropenia and febrile neutropenia; capecitabine was, however, associated with significantly more HFS than 5-FU/FA. Consistent with these findings, the probability of predefined severe (grade 3 or 4) fluoropyrimidine-related toxic effects, the primary study safety end point, was also significantly reduced with capecitabine versus 5-FU/FA [10].

Experience with agents targeting the epithelial growth factor receptor pathway shows that patients who develop skin rash have better outcomes [20–22]. A similar analysis with capecitabine in women with metastatic breast cancer [14] was, however, small,

Figure 4. Disease-free survival in patients with or without dose modifications (i.e. dose reductions, treatment interruptions or cycle delays) who received capecitabine (A) or 5-fluorouracil/folinic acid (B).
retrospective and confounded in part by the likelihood that patients with metastatic disease who responded to capecitabine would receive more cycles of treatment and be at greater risk of toxicity. Analysis of the 5-year X-ACT data suggests that the occurrence of HFS was associated with a better outcome in patients treated with capecitabine but not 5-FU/FA; patients who did not experience HFS had very similar outcomes with capecitabine and 5-FU/FA. Too few patients experienced each grade of HFS to enable a meaningful analysis of the impact of its severity. Nevertheless, the 73.8% OS seen in patients treated with capecitabine who experienced HFS of any grade is substantially higher than that of 66.3% seen in those receiving capecitabine who did not. Although post hoc (i.e. not part of the original study plan), this analysis does support the earlier report [14] and is not confounded by treatment duration, which is predetermined in the adjuvant setting and did not differ between the treatment arms.

These observations raise the possibility that HFS may be an easy to identify clinical marker for greater therapeutic efficacy with capecitabine. The precise mechanisms for this effect are unknown, although it has been suggested to be partly attributable to the three-step enzymatic activation of capecitabine [23]. In addition, a recent study suggested that a polymorphism in cytidine deaminase, one of these three enzymes, may be a predictor of severe HFS [24]. It is, however, important to note that patients who did not experience HFS still benefited from treatment with capecitabine to the same degree as those who received 5-FU/FA. Thus, lack of HFS should not be taken as an indication to withdraw capecitabine due to a perceived lack of efficacy. Rather, if confirmed, our findings emphasize the importance of correctly managing HFS should it occur (see ‘Patients and Methods’ section and Capecitabine Summary of Product Characteristics for details). Importantly, dose modifications can be carried out with the knowledge that they do not significantly reduce the efficacy of capecitabine (Figure 4A). These observations, together with recent data documenting the geographic variability of fluoropyrimidine tolerability [25], highlight the importance of titrating the dose of capecitabine to the individual patient [13].

In conclusion, the efficacy benefits observed with capecitabine adjuvant therapy at 3 years were maintained after 5 years. Oral capecitabine is, therefore, an effective, better tolerated and more convenient alternative to bolus 5-FU/FA in the adjuvant treatment of patients with stage III colon cancer, including those aged over 70 years. The hypothesis that HFS acts as a marker of efficacy warrants testing in a prospective study.

Table 4. Relationship between HFS and DFS or OS after a median follow-up of 6.9 years (intent-to-treat population)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Capecitabine (n = 1004)</th>
<th>5-Fluorouracil/folinic acid (n = 983)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HFS</td>
<td>391</td>
<td>175</td>
<td>888</td>
</tr>
<tr>
<td>HFS (grade 1–3)</td>
<td>613</td>
<td>246</td>
<td>61.3</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HFS</td>
<td>391</td>
<td>139</td>
<td>888</td>
</tr>
<tr>
<td>HFS (grade 1–3)</td>
<td>613</td>
<td>180</td>
<td>73.8</td>
</tr>
</tbody>
</table>

*Estimated from Kaplan–Meier curves.

HFS, hand–foot syndrome; DFS, disease-free survival; OS, overall survival; CI, confidence interval.

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